Rh(III)-catalyzed Enantioselective Benzamidation of Cyclopropenes

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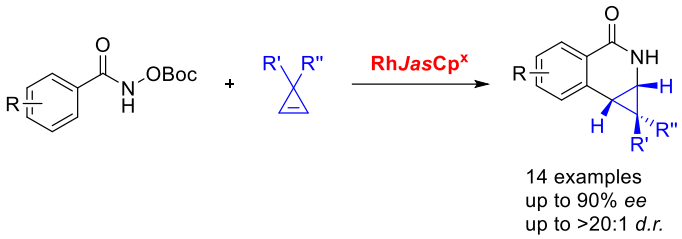


Received:
Accepted:
Published online:
DOI:

Abstract Cyclopropylamines are characteristic structural motifs found in a variety of natural products and pharmaceuticals calling for the development of new methods for their synthesis. Herein the synthesis of enantioenriched cyclopropylamines through catalytic enantioselective C-H functionalization using chiral Rh*Jas*Cp complex is reported. The reaction proceeds under mild conditions with high enantiocontrol. This reaction enables access to cyclopropylamines with three contiguous stereocenters originating from their corresponding cyclopropenes.

Key words rhodium, cyclopropene, chiral cyclopentadiene, C-H activation, cyclopropylamine

Cyclopropanes are a unique class of carbocycles due to their unusual bonding and inherent ring strain.[1] The cyclopropane unit is considered a privileged motif in medicinal chemistry. It is not only found as a basic structural element in a wide range of naturally occurring compounds but also in a variety of marketed drugs.[2] The cyclopropane unit has attracted medicinal chemists due to its impact on physiochemical properties of drugs (e.g. increased metabolic stability and permeability) without a large increase in molecular weight. Additionally, it provides opportunities to arrange groups in a rigid and specific three dimensional orientation in space.[3] Therefore, various approaches and synthetic routes for their synthesis have been developed.[4,5] In particular, aminocyclopropanes are very interesting structures that exist in biologically active natural products and synthetic drugs (Figure 1).[6] Due to their high importance, also efficient methods for the construction of enantioenriched cyclopropylamines have been developed. One typical route to obtain these compounds employs enantiopure carboxylic acids and via a Curtius rearrangement transforms them into the aminocyclopropane of interest.[7] However, this requires a multistep sequence and access to the required enantiopure acids. Alternative efficient approaches rely on the [2+1] cycloaddition reaction of *N*-substituted alkenes with diazoesters (Scheme 1a),[8] or utilize palladium(0) catalyst with chiral ligands to achieve an enantioselective C–H arylation of cyclopropanes (Scheme 1b).[9] Yet, a more common strategy employs the direct catalytic functionalization of cyclopropenes,[10] in particular their direct enantioselective hydroamination (Scheme 1c).[11]

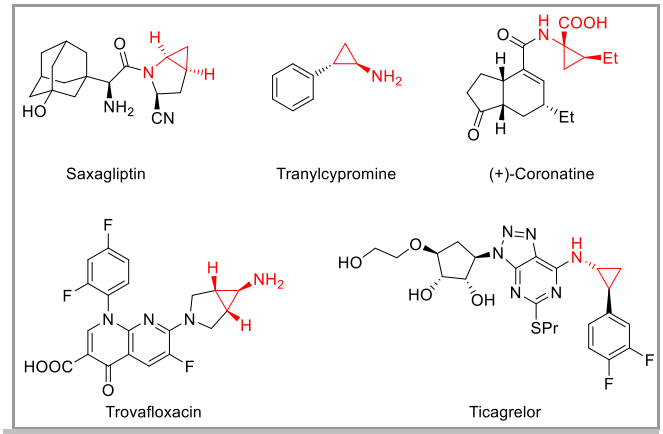
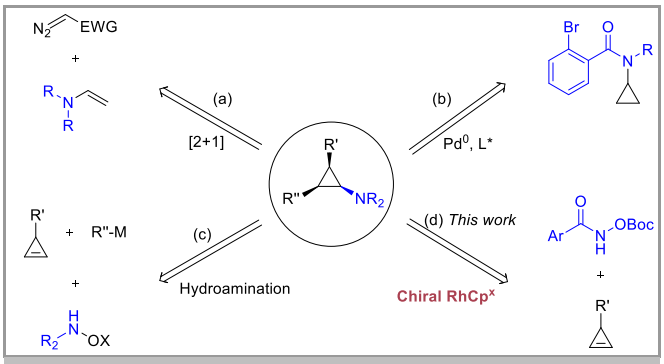


Figure 1 Selected examples of natural products and pharmaceuticals containing aminocyclopropanes.

Chiral transition-metal cyclopentadienyl (Cp^x)complexes have emerged as powerful stereodirecting catalysts in enantioselective C-H functionalization transformations,[12] and a variety of chiral Cp^x complexes have been synthesized and successfully applied in asymmetric reactions.[13,14] In 2017, Rovis *et al.* reported the diastereoselective benzamidation of cyclopropenes with aryl-hydroxamates using a bulky non-chiral Rh(III) Indene complex.[15] The reaction proceeded with high diastereocontrol. However, the enantioselective version of this transformation has not been reported.

Given this lack of methodology, we intended to apply the chiral rhodium complexes (Rh*Jas*Cp) developed earlier by us in this transformation in order to achieve an enantio- and diastereoselective benzamidation of cyclopropenes (Scheme 1d). This method would open up a new opportunity to access

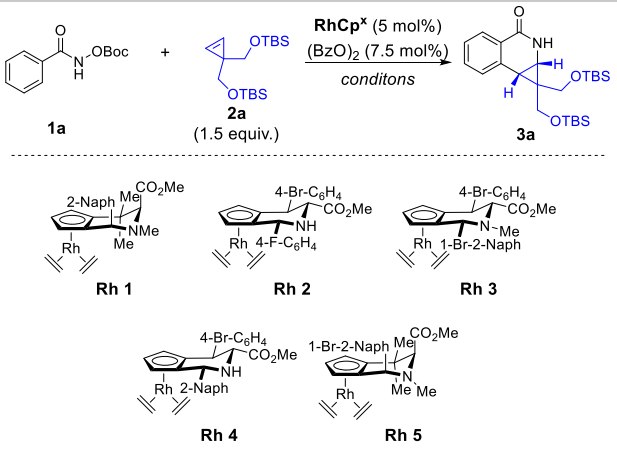
enantioenriched, fully substituted aminocyclopropanes with three contiguous stereogenic centers.



Scheme 1 Enantioselective cyclopropylamines formation strategies.

For method development OBoc-phenyl hydroxamate **1a** and symmetric cyclopropene **2a**[16] were chosen as model substrates (Table 1). As shown in Table 1, chiral catalyst **Rh 1** led to the formation of the desired product with moderate yield and enantioselectivity (entry 1). Lowering te reaction temperature to -5 °C led to lower reactivity with little influence on the *ee* (entry 2). Screening of a variety of other solvents (entries 3-5) demonstrated that MeOH was best in terms of *ee* and yield. Screening of catalysts (entries 6-9), showed that **Rh 4** yielded the desired product in very good yield and enantioselectivity (entry 9). Finally, further solvent screening (entries 10-13) led to the most favorable conditions, i.e. a (1:1) mixture of MeOH:DCM. Under these conditions the desired product was obtained in good yield and high *ee* (entry 12).

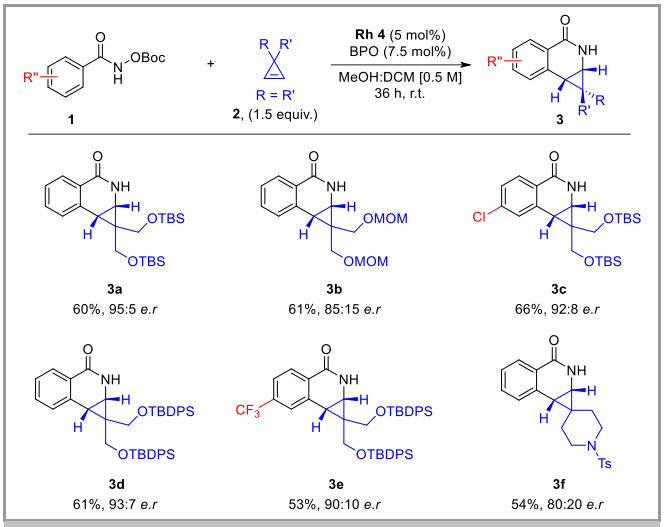
Table 1 Optimization of conditions for the enantioselective benzamidation of cyclopropenes.



Entry	Catalyst	Solvent	Temp	Yield (%)	er
1	**Rh 1**	MeOH	23	45	86.5:13.5
2	**Rh 1**	MeOH	-5	30	88.5:11.5
3	**Rh 1**	*i*PrOH	23	49	87:13
4	**Rh 1**	DCM	23	50	75:25
5	**Rh 1**	HFIP	23	64	74:26
6	**Rh 2**	MeOH	23	33	84:16
7	**Rh 3**	MeOH	23	46	79.5:20.5
8	**Rh 4**	MeOH	23	46	93.5:6.5
9	**Rh 5**	MeOH	23	54	89:11
10	**Rh 4**	DCM	23	28	93:7
11	**Rh 4**	MeOH: DCM (4:1)	23	56	94:6
12	**Rh 4**	MeOH: DCM (1:1)	23	60	95:5
13	**Rh 4**	TFE: DCM (1:1)	23	58	92:8

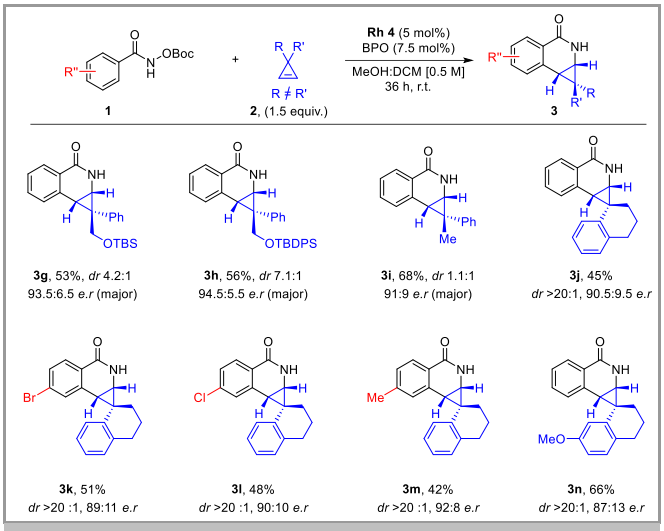
Reactions were run for 36 h at [0.5] M. Yields were determined for isolated products. *ee* were determined using chiral HPLC.

With the optimized reaction conditions in hand the scope of the transformation for substrates was explored. As shown in Scheme 2, symmetric cyclopropenes with different protecting groups on the oxygen led to the formation of the desired products (**3a-3e**) in good yields and enantioselectivities. Spiro-cyclopropene afforded the desired cyclopropylamide **3f** in viable yield with moderate *ee*.



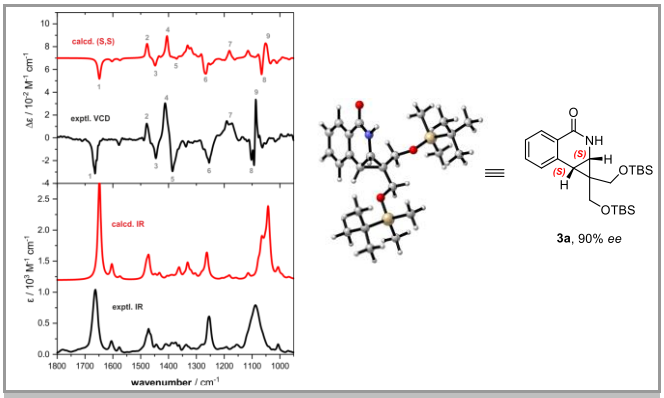
Scheme 2 Substrate scope for the enantioselective Rh*Jas*Cp-catalyzed benzamidation with symmetric cyclopropenes.

Investigateion of non-symmetric cyclopropenes (Scheme 3) revealed that cyclopropylamides **3g-3i** were obtained in good yield and *ee*, but with moderate to low diastereoselectivity. However, surprisingly, cyclopropylamide **3j** was formed in good yield and *ee* and with high diastereoselectivity (>20:1). Further derivatives bearing different substituents on the aryl-hydroxamate (**3k-3m**) and the cyclopropane (**3n**) yielded the final products with both viable *ee* and d.r.



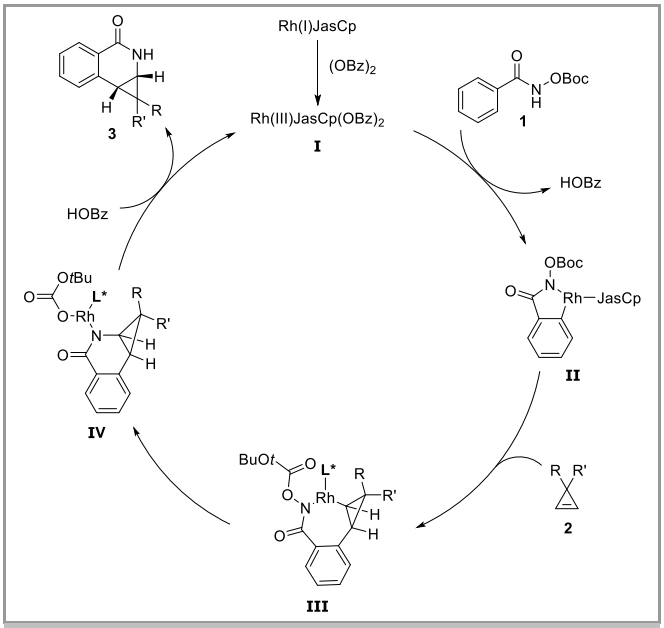
Scheme 3 Substrate scope for the enantioselective Rh*Jas*Cp-catalyzed benzamidation with non-symmetric cyclopropenes.

The absolute configuration of compound **3a** was determined to be (*S,S*) by means of vibrational circular dichroism (VCD) spectroscopy.[17] Scheme 4 shows the experimental IR and VCD spectra obtained for **3a** alongside the computationally predicted results for the (*S,S*)-enantiomer. The computational spectra are generated based on the single-conformer spectra of more than 20 conformers with one being clearly the most dominant one (Scheme 4, right; 45.4 % population according to ΔG_{298K}). Qualitative visual comparison suggests a very good match between experimental and theorical spectra, thus suggesting that the (*S,S*)-configuration assumed for the calculation is indeed the correct configuration of **3a**.



Scheme 4 Left: Experimental and calculated IR and VCD spectra of (*S,S*)-**3a** (0.17 M, $CDCl_3$, 100µm path length). Right: Lowest energy conformation.

On the basis of previous studies,[13f,15] we proposed the mechanism shown in Scheme 5 for this transformation. The reaction begins with the formation of the active Rh(III) species **I.** Subsequent oxidative addition leads to the formation of the five-membered ring rhodacycle **II**. Insertion of the cyclopropane furnishes the seven-membered ring rhodacycle **III** which undergoes reductive elimination to give intermediate **IV**. Upon hydrolysis of **IV**, the desired cyclopropylamide **3** is formed.



Scheme 5 Proposed mechanism for the benzamidation of cyclopropenes.

In conclusion we have developed the first enantioselective benzamidation of cyclopropenes using chiral Rh*Jas*Cp complexes. The cyclopropylamides were formed with preparatively viable enantio- and diastereocontrol.

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Unless otherwise noted, all commercially available compounds were used as provided without further purification. Solvents for chromatography were technical grade.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium plates with F_{-254} indicator. Compounds were visualized by irradiation with UV light or potassium permanganate staining. Column chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm).

^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR were recorded on a Bruker DRX400 (400 MHz), Bruker DRX500 (500 MHz), INOVA500 (500 MHz) and Bruker DRX700 using $CDCl_3$ as solvent ($CDCl_3$: δ = 7.26 ppm for ^{1}H-NMR, δ = 77.16 ppm for ^{13}C-NMR). Multiplicities are indicated br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (J) are given in Hertz (Hz).

High resolution mass spectra (HR-MS) were recorded on an LTQ Orbitrap mass spectrometer coupled to an Accela HPLC-System (HPLC column: Hypersyl GOLD, 50 mm x 1 mm, particle size 1.9 µm, ionization method: electron spray ionization). Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a Bruker Tensor 27 spectrometer (ATR, neat) and are reported in terms of frequency of absorption (cm^{-1}). The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase column (CHIRALCEL IC, CHIRALCEL IA; eluent: *i*-PrOH / *iso*-hexanes; 4.6 mm x 250 mm, particle size 5 µm). The chiral HPLC methods were calibrated with the corresponding racemic mixtures.

Aryl-hydroxamates **1**,[13c,14j] cyclopropenes **2**[18] and Rh-catalysts[13f,14g] were prepared according to the previously reported procedures and their characterizations match the ones reported.

Procedure for the preparation of cyclopropane 2b:

Following the procedure reported by Lautens *et al.*[18a] a solution of cyclopropene diol (1.0 equiv., 0.5 mmol, 50 mg) and *N,N*-diisopropylethylamine (3.0 equiv., 1.5 mmol, 261 µl) dissolved in 5 ml dry DCM [0.1 M] was cooled down to 0 °C. MOMCl (3.0 equiv., 1.5 mmol, 117 µl) was added and the mixture was stirred at RT for 16h. The mixture was then quenched with saturated solution $NaHCO_3$. Organic layer was separated and the aqueous layer was extracted again with DCM. The

combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude was purified on column chromatography using Pent: EtOAc as eluent (5:1) to give the desired products **2b**.

3,3-bis((methoxymethoxy)methyl)cycloprop-1-ene (2b)

Colorless oil, 75 mg, 80% yield. (5:1 Pent: EtOAc).

IR: 3022, 2948, 1519, 1371, 1224, 1109, 1015, 937, 886 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.26 (s, 2H), 4.52 (s, 4H), 3.46 (s, 4H), 3.25 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 116.0(2C), 96.2(2C), 73.7(2C), 55.1(2C), 23.9.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_9H_{17}O_4$: 189.1127; found: 189.1120.

Procedure for the preparation of cyclopropane 2h:

Following the procedure reported by Lautens *et al.*[18a] a solution of (1-phenylcycloprop-2-en-1-yl)methanol (1.0 equiv., 0.34 mmol, 50 mg) and imidazole (1.5 equiv., 0.5 mmol, 35 ml) dissolved in 5 ml dry DCM [0.1 M] was cooled down to 0 °C. TBDPSCl (2.0 equiv., 0.68 mmol, 180 µl) was added and the mixture was stirred at RT for 16h. The mixture was then quenched with saturated solution $NaHCO_3$. Organic layer was separated and the aqueous layer was extracted again with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude was purified on column chromatography using Pent as eluent to give the desired products **2h**.

***tert*-butyldiphenyl((1-phenylcycloprop-2-en-1-yl)methoxy)silane (2h)**

Colorless oil, 130 mg, 97% yield. (Pent).

IR: 3076, 2929, 1649, 1427, 1377, 1190, 1035, 997, 847 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.60 – 7.53 (m, 4H), 7.38 – 7.32 (m, 2H), 7.32 – 7.26 (m, 4H), 7.24 – 7.13 (m, 4H), 7.10 – 7.07 (m, 1H), 7.05 (s, 2H), 4.05 (s, 2H), 0.96 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 146.8, 135.7(3C), 134.0, 129.5(2C), 127.8(2C), 127.5(3C), 126.6(2C), 125.4, 112.8(2C), 69.6, 28.9, 26.9(3C), 19.3.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{26}H_{29}OSi$: 385.1988; found: 385.1982.

General procedure for the enantioselective synthesis of cyclopropylamides 3

Without any protection from air, catalyst **Rh4** (5 mol %) and BPO (7.5 mol %) were weighed in a dram vial filled with a magnetic stirrer bar. Aryl-hydroxymate **1** (1.0 eq., 0.05 mmol) was added and the mixture was dissolved in a (1:1) mixture of MeOH: DCM [0.5 M]. To the stirred mixture at room temperature, cyclopropene **2** (1.5 eq., 0.075mmol) was added and the mixture was further stirred at the same temperature for 36 h. Then the solvent was removed under reduced pressure and the crude mixture was directly submitted to column chromatography using Pent: EtOAc as eluent (5:1 to 1:1) to give the desired products **3**.

(1aS,7bS)-1,1-bis(((*tert*-butyldimethylsilyl)oxy)methyl)-1,1a,2,7b-tetrahydro-3H-cyclopropa[c]isoquinolin-3-one (3a)

Colorless oil, 13,3 mg, 60% yield. (5:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = -62.5 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 2/98, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 33.5 min; minor enantiomer: t_R = 57.7 min, 90% ee

IR: 3176, 2880, 1788, 1573, 1461, 1250, 1023, 962, 860 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.51 – 8.44 (m, 1H), 7.80 (td, J = 6.9, 0.8 Hz, 1H), 7.70 – 7.62 (m, 2H), 6.48 (s, 1H), 4.17 (d, J = 10.1 Hz, 1H), 4.02 (d, J = 10.2 Hz, 1H), 3.83 (d, J = 11.2 Hz, 1H), 3.66 (d, J = 11.2 Hz, 1H), 3.57 (dd, J = 8.6, 3.2 Hz, 1H), 2.72 (d, J = 8.5 Hz, 1H), 1.26 (s, 9H), 1.10 (s, 9H), 0.43 (s, 6H), 0.17 (s, 3H), 0.00 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.9, 136.3, 132.4, 129.6, 128.0, 127.5, 126.7, 63.9, 56.6, 36.8, 27.6, 25.9(3C), 25.7(3C), 21.1, 18.3, -5.3(2C), -5.7(2C), -6.1(2C).

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{24}H_{42}O_3NSi_2$: 448.2703; found: 448.2694.

(1aS,7bS)-1,1-bis((methoxymethoxy)methyl)-1,1a,2,7b-tetrahydro-3H-cyclopropa[c]isoquinolin-3-one (3b)

Yellow oil, 9.4 mg, 61% yield. (2:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = -53.1 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 27.6 min; minor enantiomer: t_R = 55.2 min, 70% ee

IR: 3176, 2924, 1660, 1485, 1309, 1149, 1046, 1017, 972, 855 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.07 (dd, J = 7.8, 1.5 Hz, 1H), 7.40 (td, J = 7.5, 1.4 Hz, 1H), 7.34 (dd, J = 7.8, 1.4 Hz, 1H), 7.28 (td, J = 7.5, 1.4 Hz, 1H), 6.41 – 6.37 (m, 1H), 4.61 (d, J = 1.3 Hz, 2H), 4.37 (d, J = 6.6 Hz, 1H), 4.28 (d, J = 6.7 Hz, 1H), 3.62 (d, J = 10.3 Hz, 1H), 3.53 (d, J = 10.3 Hz, 1H), 3.35 (d, J = 11.1 Hz, 1H), 3.34 (s, 3H), 3.30 – 3.17 (m, 2H), 2.99 (s, 3H), 2.42 (d, J = 8.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.6, 135.2, 132.6, 129.5, 128.2, 127.1, 126.3, 96.5(2C), 69.8, 61.8, 55.4, 54.8, 37.4, 24.6, 22.5.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{16}H_{22}O_5N$: 308.1498; found: 308.1494.

(1aS,7bS)-1,1-bis(((*tert*-butyldimethylsilyl)oxy)methyl)-6-chloro-1,1a,2,7b-tetrahydro-3H-cyclopropa[c]isoquinolin-3-one (3c)

Yellow oil, 15.8 mg, 66% yield. (5:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = +11.5 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 5/95, flow rate = 0.5 mL min^{-1}, minor enantiomer: t_R = 14.1 min; major enantiomer: t_R = 19.1 min, 84% ee

IR: 2954, 1672, 1462, 1360, 1252, 1033, 1006, 936 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.96 (d, J = 8.3, 2H), 7.42 – 7.33 (m, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.20 (dd, J = 8.4, 2.1 Hz, 1H), 6.96 (s, 1H), 3.77 (d, J = 10.1 Hz, 1H), 3.59 (d, J = 10.1 Hz, 1H), 3.40 (d, J = 11.3 Hz, 1H), 3.23 – 3.15 (m, 2H), 2.26 (d, J = 8.4 Hz, 1H), 0.83 (s, 9H), 0.67 (s, 9H), 0.00 (s, 6H), -0.25 (s, 3H), -0.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 163.7, 138.7, 133.3, 130.0, 129.5, 128.4, 124.7, 63.6, 56.6, 36.1, 27.9, 25.9(3C), 25.6(3C), 20.7, 18.3, 14.2, -5.3(2C), -5.8(2C), -6.2(2C).

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{24}H_{41}O_3NClSi_2$: 482.2313; found: 482.2304.

(1aS,7bS)-1,1-bis((*tert*-butyldiphenylsilyl)methyl)-1,1a,2,7b-tetrahydro-3H-cyclopropa[c]isoquinolin-3-one (3d)

Dark-yellow oil, 22.6 mg, 61% yield. (5:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = -3.5 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 10/90, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 14.7 min; major enantiomer: t_R = 26.8 min, 86% ee

IR: 3049, 2856, 1681, 1471, 1389, 1252, 1112, 1007, 936 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.01 (dd, J = 7.8, 1.5 Hz, 1H), 7.64 – 7.56 (m, 3H), 7.48 – 7.41 (m, 2H), 7.44 – 7.19 (m, 14H), 7.14 – 7.07 (m, 2H), 7.06 – 7.01 (m, 2H), 5.72 (s, 1H), 4.06 (d, J = 10.4 Hz, 1H), 3.64 (d, J = 11.3 Hz,

1H), 3.60 (d, J = 10.5 Hz, 1H), 3.32 (d, J = 11.3 Hz, 1H), 2.79 (dd, J = 8.6, 3.2 Hz, 1H), 2.20 (d, J = 8.6 Hz, 1H), 0.99 (s, 9H), 0.81 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.4, 135.7(4C), 135.6(4C), 135.4(6C), 135.2(6C), 132.4, 129.9, 129.5, 129.4, 128.1, 127.8(2C), 127.7(2C), 127.6(2C), 57.4, 27.9, 26.9(3C), 26.6(3C), 21.2, 19.3, 19.1.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{44}H_{50}O_3NSi_2$: 696.3329; found: 696.3326.

(1aS,7bS)-1,1-bis(((*tert*-butyldiphenylsilyl)oxy)methyl)-6-(trifluoromethyl)-1,1a,2,7b-tetrahydro-3H-cyclopropa[c]isoquinolin-3-one (3e)

Orange oil, 20 mg, 53% yield. (4:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = -61.7 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 5/95, flow rate = 0.5 mL min^{-1}, minor enantiomer: t_R = 13.4 min; major enantiomer: t_R = 19.2 min, 80% ee

IR: 2928, 2159, 1673, 1471, 1389, 1128, 1033, 936, 887 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.07 (d, J = 8.1 Hz, 1H), 7.65 – 7.57 (m, 4H), 7.44 – 7.34 (m, 7H), 7.35 (d, J = 1.4 Hz, 2H), 7.30 – 7.24 (m, 1H), 7.11 (t, J = 7.6 Hz, 2H), 7.07 – 7.01 (m, 2H), 6.76 (s, 1H), 4.06 (d, J = 10.5 Hz, 1H), 3.69 (d, J = 10.5 Hz, 1H), 3.60 (d, J = 11.5 Hz, 1H), 3.25 (d, J = 11.5 Hz, 1H), 2.94 (dd, J = 8.5, 3.3 Hz, 1H), 2.23 (d, J = 8.5 Hz, 1H), 1.01 (s, 9H), 0.77 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.7, 162.8, 137.1, 135.7, 135.6, 135.4, 135.1(2C), 134.0, 133.8, 133.4(2C), 133.1, 132.8, 132.5, 130.1, 130.1, 130.0, 129.6, 129.5, 129.1, 128.6, 128.4, 127.9, 127.9, 127.7, 127.6, 126.5, 124.6, 122.4, 64.5, 57.3, 37.1, 28.2, 26.9(3C), 26.5(3C), 20.8, 19.3, 19.0.

^{19}F NMR ($CDCl_3$, 470 MHz): δ = -63.14.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{45}H_{49}O_3NF_3Si_2$: 764.3203; found: 764.3201.

(1aS,7bS)-1'-tosyl-1a,7b-dihydrospiro[cyclopropa[c]isoquinoline-1,4'-piperidin]-3(2H)-one (3f)

Yellow oil, 10.3 mg, 54% yield. (1:2 Pent: EtOAc). $[\alpha]_D^{RT}$ = -44.1 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1}, minor enantiomer: t_R = 35.1 min; major enantiomer: t_R = 37.8 min, 60% ee

IR: 2915, 1650, 1576, 1352, 1290, 1167, 1089, 1019, 952, 907 cm^{-1}.

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.02 (dd, J = 7.8, 1.4 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.36 (td, J = 7.5, 1.4 Hz, 1H), 7.28 – 7.23 (m, 3H), 7.13 (dd, J = 7.7, 1.2 Hz, 1H), 6.20 (s, 1H), 3.17 (ddd, J = 11.1, 6.8, 3.6 Hz, 1H), 2.95 (ddd, J = 11.6, 8.0, 3.4 Hz, 1H), 2.90 (dd, J = 8.6, 3.2 Hz, 1H), 2.82 (ddd, J = 11.4, 6.8, 3.6 Hz, 1H), 2.68 (ddd, J = 11.7, 8.1, 3.6 Hz, 1H), 2.39 (s, 3H), 2.06 (d, J = 8.5 Hz, 1H), 1.64 (dt, J = 17.3, 3.6 Hz, 0H), 1.47 (ddd, J = 13.3, 6.9, 3.4 Hz, 1H), 1.37 – 1.28 (m, 1H), 1.25 – 1.20 (m, 1H).

^{13}C NMR ($CDCl_3$, 175 MHz): δ = 163.5, 143.6, 135.4, 133.2, 132.6, 129.7(2C), 129.2, 128.2, 127.6(2C), 127.0, 126.2, 45.3, 45.2, 38.5, 33.8, 24.1, 22.4, 21.5, 21.1.

HRMS (???): *m/z* [M + H]$^+$ calcd for $C_{21}H_{23}O_3N_2S$: 383.1429; found: 383.1425.

1-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-phenyl-1,1a,2,7b-tetrahydro-3H-cyclopropa[c]isoquinolin-3-one (3g)

Yellow oil, 11.7 mg, 53% yield. (3:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = -22.4 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 5/95, flow rate = 0.5 mL min^{-1}, Major isomer: major enantiomer: t_R = 37.2 min; minor enantiomer: t_R = 66.5 min, 87% ee. Minor isomer, minor enantiomer: t_R = 59.3 min; minor enantiomer: t_R = 72.7 min, 87% ee

IR: 3033, 2852, 1655, 1575, 1402, 1251, 1123, 1058, 985, 906 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.17 (d, J = 7.9 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.55 – 7.49 (m, 4H), 7.40 (d, J = 19.5 Hz, 2H), 7.21 (d, J = 16.4 Hz, 1H), 7.10 (d, J = 6.3 Hz, 3H), 6.97 – 6.95 (m, 2H), 3.89 (q, J = 7.2 Hz, 2H), 3.71 – 3.60 (m, 1H), 2.92 (d, J = 8.5 Hz, 1H), 0.93 (s, 9H), 0.00 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 164.3, 137.4, 133.2, 132.7, 132.6, 132.4, 130.0, 129.2, 128.8, 128.3, 128.1, 127.9, 126.3, 67.8, 60.4, 40.0, 33.0, 25.8(3C), 18.3, -5.5, -5.6.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{23}H_{30}O_2NSi$: 380.2046; found: 380.2041.

1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-phenyl-1,1a,2,7b-tetrahydro-3H-cyclopropa[c]isoquinolin-3-one (3h)

Yellow oil, 15 mg, 56% yield. (3:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = +5.6 (CH_2Cl_2, c = 1.00).

HPLC conditions (for major isomer): CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 3/97, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 35.0 min; minor enantiomer: t_R = 50.1 min, 89% ee

IR: 3048, 2855, 1691, 1574, 1390, 1194, 1027, 935, 822 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.12 (dd, J = 7.8, 1.4 Hz, 1H), 7.51 (dd, J = 7.6, 1.3 Hz, 1H), 7.50 – 7.41 (m, 3H), 7.35 (tdd, J = 7.6, 4.7, 2.7 Hz, 3H), 7.31 – 7.25 (m, 1H), 7.29 – 7.17 (m, 3H), 7.16 – 7.09 (m, 2H), 7.07 (dd, J = 8.3, 6.9 Hz, 2H), 6.91 – 6.84 (m, 2H), 6.58 (s, 1H), 3.59 (d, J = 11.3 Hz, 1H), 3.52 – 3.46 (m, 2H), 2.78 (d, J = 8.7 Hz, 1H), 0.71 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.7, 141.8, 135.3(2C), 135.1(2C), 132.7, 132.6, 129.9(3C), 129.4, 129.3, 128.4(2C), 128.1, 127.5(3C), 127.4, 127.3, 127.1, 61.6, 39.8, 32.2, 26.3(3C), 24.9, 18.9.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{33}H_{34}O_2NSi$: 504.2359; found: 504.2348.

(1S,1aS,7bS)-1-methyl-1-phenyl-1,1a,2,7b-tetrahydro-3H-cyclopropa[c]isoquinolin-3-one (3i)

Colorless oil, 8.4 mg, 68% yield. (1:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = -60.1 (CH_2Cl_2, c = 1.00).

HPLC conditions (for major isomer): CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 3/97, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 44.4 min; minor enantiomer: t_R = 53.4 min, 82% ee

IR: 3036, 1656, 1478, 1369, 1250, 1158, 1090, 980, 912, 838 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.16 (d, J = 7.9 Hz, 1H), 7.43 (td, J = 7.5, 1.5 Hz, 1H), 7.43 – 7.32 (m, 1H), 7.36 – 7.22 (m, 5H), 7.22 – 7.14 (m, 1H), 6.94 (s, 1H), 3.41 (dd, J = 8.9, 3.4 Hz, 1H), 2.64 (d, J = 8.9 Hz, 1H), 1.06 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.4, 145.0, 136.6, 132.7(2C), 129.7(2C), 128.9, 128.4, 127.2(2C), 127.0, 126.7, 40.9, 26.8, 25.1, 13.3.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{17}H_{16}ON$: 250.1232; found: 250.1226.

(1aS,7bS)-1a,3',4',7b-tetrahydro-2'H-spiro[cyclopropa[c]isoquinoline-1,1'-naphthalen]-3(2H)-one (3j)

Colorless oil, 6.1 mg, 45% yield. (3:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = -28.1 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 16.6 min; major enantiomer: t_R = 23.3 min, 81% ee

IR: 3067, 2929, 1700, 1576, 1391, 1238, 1158, 1081, 1022, 987, 914 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.11 (dd, J = 7.8, 1.5 Hz, 1H), 7.41 (td, J = 7.5, 1.4 Hz, 1H), 7.37 – 7.22 (m, 2H), 7.18 – 7.10 (m, 1H), 7.13 – 7.02 (m, 2H), 6.67 (s, 1H), 6.61 (d, J = 7.9 Hz, 1H), 3.43 (dd, J = 8.7, 3.1 Hz, 1H), 2.76

(t, J = 6.2 Hz, 2H), 2.72 (d, J = 8.7 Hz, 1H), 1.68 – 1.55 (m, 1H), 1.59 – 1.47 (m, 1H), 1.32 – 1.14 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 139.0, 138.0, 136.1, 132.6, 129.5(2C), 129.0, 128.1, 127.1(2C), 126.6, 125.3, 121.0, 43.7, 30.7, 30.3, 22.8, 21.6, 21.3.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{19}H_{18}ON$: 276.1388; found: 276.1384.

(1aS,7bS)-6-bromo-1a,3',4',7b-tetrahydro-2'H-spiro[cyclopropa[c]isoquinoline-1,1'-naphthalen]-3(2H)-one (3k)

Orange oil, 8.2 mg, 51% yield. (2:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = -18.5 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1}, minor enantiomer: t_R = 30.1 min; major enantiomer: t_R = 58.4 min, 78% ee

IR: 3022, 2858, 1651, 1428, 1308, 1114, 1009, 974, 880 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.97 (d, J = 8.2 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.14 (ddd, J = 7.8, 6.5, 2.4 Hz, 2H), 7.13 – 7.03 (m, 2H), 6.57 (d, J = 7.9 Hz, 1H), 6.40 (s, 1H), 4.05 (d, J = 7.1 Hz, 1H), 2.77 (t, J = 6.2 Hz, 2H), 2.66 (d, J = 8.6 Hz, 1H), 1.69 – 1.54 (m, 2H), 1.31 – 1.20 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.6, 138.4, 138.0, 133.3, 132.3, 130.5, 130.0, 129.8, 129.0, 128.4, 127.6, 126.7, 125.6, 125.6, 121.0, 60.4, 43.8, 30.6, 29.8, 23.2, 21.3.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{19}H_{17}ONBr$: 354.0494 and 356.0473; found: 354.0490 and 356.0469.

(1aS,7bS)-6-chloro-1a,3',4',7b-tetrahydro-2'H-spiro[cyclopropa[c]isoquinoline-1,1'-naphthalen]-3(2H)-one (3l)

Yellow oil, 7.4 mg, 48% yield. (1:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = -39.1 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1}, minor enantiomer: t_R = 29.4 min; major enantiomer: t_R = 57.5 min, 80% ee

IR: 3029, 1651, 1435, 1252, 1130, 1022, 993, 911 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07 – 8.00 (m, 1H), 7.26 (d, J = 7.7 Hz, 2H), 7.18 – 7.09 (m, 1H), 7.13 – 7.02 (m, 2H), 6.68 (s, 1H), 6.62 – 6.55 (m, 1H), 3.44 (dd, J = 8.6, 3.3 Hz, 1H), 2.77 (t, J = 6.1 Hz, 2H), 2.66 (d, J = 8.7 Hz, 1H), 1.69 – 1.47 (m, 2H), 1.32 – 1.14 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.7, 138.8, 138.4, 138.0, 137.9, 129.7, 129.3, 129.0, 127.5, 126.7, 125.5, 121.0, 43.8, 30.6, 29.9, 23.4, 21.6, 21.3.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{19}H_{17}ONCl$: 310.0999; found: 310.0995.

(1aS,7bS)-6-methyl-1a,3',4',7b-tetrahydro-2'H-spiro[cyclopropa[c]isoquinoline-1,1'-naphthalen]-3(2H)-one (3m)

Colorless oil, 6 mg, 42% yield. (2:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = -28.0 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, minor enantiomer: t_R = 35.3 min; major enantiomer: t_R = 68.5 min, 84% ee

IR: 3027, 2853, 1599, 1368, 1274, 1130, 1036, 987, 942, 861 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.06 – 7.96 (m, 1H), 7.43 – 7.34 (m, 1H), 7.18 – 7.02 (m, 5H), 6.59 (d, J = 7.8 Hz, 1H), 3.42 (dd, J = 8.7, 3.3 Hz, 1H), 2.76 (t, J = 6.2 Hz, 2H), 2.67 (d, J = 8.7 Hz, 1H), 2.31 (s, 3H), 1.66 – 1.46 (m, 2H), 1.31 – 1.16 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.7, 130.1, 130.0, 128.9, 128.4, 128.1, 126.6, 125.9, 125.3, 121.7, 121.0, 119.1, 43.7, 41.1, 30.8, 30.7, 30.3, 22.5, 21.6, 21.2.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{20}H_{20}ON$: 290.1545; found: 290.1540.

(1aS,7bS)-7'-methoxy-1a,3',4',7b-tetrahydro-2'H-spiro[cyclopropa[c]isoquinoline-1,1'-naphthalen]-3(2H)-one (3n)

Red oil, 10.7 mg, 66% yield. (1:1 Pent: EtOAc). $[\alpha]_D^{RT}$ = -6.5 (CH_2Cl_2, c = 1.00).

HPLC conditions: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 13.9 min; minor enantiomer: t_R = 23.1 min, 74% ee

IR: 2930, 1664, 1554, 1403, 1325, 1171, 1095, 1048, 994, 890, 828 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.11 (dd, J = 7.8, 1.5 Hz, 1H), 7.50 (ddt, J = 8.8, 6.9, 1.4 Hz, 0H), 7.45 – 7.34 (m, 1H), 7.34 – 7.22 (m, 2H), 7.19 (s, 1H), 6.98 (dt, J = 8.5, 1.0 Hz, 1H), 6.64 (dd, J = 8.3, 2.6 Hz, 1H), 6.15 (d, J = 2.5 Hz, 1H), 3.73 (s, 3H), 3.42 (dd, J = 8.7, 3.5 Hz, 1H), 2.71 – 2.66 (m, 3H), 1.59 – 1.48 (m, 3H), 1.29 – 1.12 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.4, 158.5, 140.3, 136.0, 132.7, 130.2, 129.7, 129.5, 128.3, 128.1, 127.1, 110.3, 107.5, 55.4, 43.7, 30.3, 29.8, 22.8, 21.8, 21.2.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{20}H_{20}O_2N$: 306.1494; found: 306.1492.

Experimental and computational details for the VCD measurement of 3a.

Experimental IR and VCD spectra were recorded on a Bruker Vertex 70 equipped with a PMA 50 module for VCD measurements. **3a** was dissolved in chloroform-d_1 at a concentration of 0.17 M and filled into a BaF_2-IR cell with 100 μm path length. The VCD spectrum was accumulated over 10 hours (40k scans) and baseline correction was carried out by subtraction of the solvent spectrum recorded under identical conditions. Spectra calculations were performed in a two-step process. First, a conformational analysis was carried out at molecular force field level (MMFF[19a] using Spartan 14[19b]). In the second step, the resulting conformers were subjected to further geometry optimization and vibrational spectra calculations at B3LYP/6-311++G(2d,p)/IEFPCM($CHCl_3$) level using Gaussian 09.[19c] The IR and VCD spectra were simulated based on the relative Gibbs free energies ΔG_{298K} of the optimized conformers and assuming a Lorentzian shaped line broadening (6 cm^{-1} half-width at half-height). Finally, the frequencies were scaled by a factor of 0.98 in order to account for errors introduced by the harmonic approximation.

Acknowledgment

This work was supported by the Max-Planck-Gesellschaft. S.S. thanks the Alexander von Humboldt Foundation for funding. H.L. is grateful to the Swiss National Science Foundation (SNSF) for an Early Postdoc. Mobility fellowship (P2GEP2_168250). This work has been funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) through the Heisenberg programme (ME 4267/5-1; project no. 418661145).

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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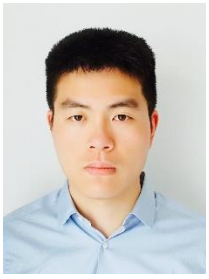
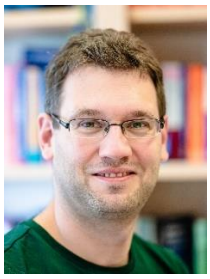
Biosketches

	Saad Shaaban completed his Bachelor studies at the university of Damascus-Syria in 2008. In 2011, he moved to Germany where he did his Master studies at Ruhr University Bochum followed by a Master thesis at the Max-Planck Institute for Coal research in Mülheim a. d. Ruhr. In 2013, he started his PhD in the University of Vienna with Prof. Nuno Maulide. Since 2018, he is a post-doctoral researcher, supported by an Alexander von Humboldt fellowship, with Prof. Herbert Waldmann at the Max Planck Institute of Molecular Physiology in Dortmund, working on the applications of chiral *Jas*Cp complexes in new transformations.
	Houhua Li was born in Jiangxi, China, in 1985. In 2009, after obtaining his B.Sc. and M.Sc. at Peking University (China), he moved to National Institute of Biological Sciences (NIBS) in Beijing working with Prof. Xiaoguang Lei on natural product synthesis. He received his PhD under the supervision of Prof. Clément Mazet at the University of Geneva (Switzerland) in 2016 and subsequently conducted his postdoc with Prof. Herbert Waldmann at the Max Planck Institute of Molecular Physiology. In April 2019, he returned to Peking University to start his own independent academic career, focusing on the translational research on bioactive natural products
	Christian Merten studied chemistry at the University of Bremen, Germany, and received his Diploma (equivalent to MSc, 2007) and PhD (2010) for work with A. Hartwig at the Fraunhofer Institute for Advanced Materials (IFAM) in Bremen. He worked at the University of Alberta in Edmonton, Canada, as Feodor Lynen Postdoctoral Fellow of the Alexander von Humboldt foundation in the lab of Y. Xu (2011-2013). Afterwards, he joined the Faculty of Chemistry and Biochemistry at the Ruhr-University Bochum (RUB) as an independent research group leader with a Liebig Fellowship of the Fonds der Chemischen Industrie (FCI). Since 2019 he is Heisenberg fellow of the Deutsche Forschungsgemeinschaft (DFG) and was appointed as Heisenberg professor for Stereochemistry and Chiroptical Spectroscopy in 2020. Christian is expert in absolute configuration determination by chiroptical spectroscopy and studies stereoselective intermolecular interactions in catalysis and chiral separation techniques as well as fundamental aspects of probing stereochemistry under cryogenic conditions.
	Andrey P. Antonchick received his PhD from the Institute of Bioorganic Chemistry of the National Academy of Sciences of Belarus (Minsk, Belarus) and the Max Planck Institute for Chemical Ecology (Jena, Germany) under the guidance of Prof. V. A. Khripach and Dr. B. Schneider. After a postdoctoral appointment with Prof. M. Rueping at Frankfurt University, he joined the group of Prof. H. Waldmann. He was appointed group leader at the Max Planck Institute of Molecular Physiology and TU Dortmund. In 2020, he accepted the position of Associate Professor at the Nottingham Trent University. His research interests lie in the development of new reaction methodologies.
	Herbert Waldmann obtained his PhD in organic chemistry in 1985 under the supervision of Horst Kunz. After a postdoctoral period with George Whitesides at Harvard University, he returned to the University of Mainz and completed his habilitation in 1991. He was appointed as director at the MPI Dortmund and professor of Organic Chemistry at TU Dortmund University in 1999. His research focuses on the syntheses of natural-product-derived compounds and their biological evaluation.

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